cholesterol.

DR. COHEN: Okay. You have to look at the system as it exists today. I'm a clinician. I see patients every day, and so what we have is a system whereby people either come in and see us and we define their risks for them or they don't, and hopefully when they see this package on the shelf it will say, "See your physician if this product is right for you."

If they don't and they take it anyway, I would submit to you, in my own estimation, and I'm speaking now not from science, but from my best guess, that they will benefit from having a lower lipid therapy, a lower lipid level in the context of the other risk factors, let us say, hypertension and smoking, than they would had they not bought the drug.

But hopefully, when they see that package, it will drive them into their physician who will then say to him or her, you know, "This product is right," or not right. "You're multiple risk. You need to be on a higher dose," or whatever.

DR. DeLAP: Dr. Ganley.

DR. GANLEY: Yeah, I guess the question that I have then is if the individuals with the higher cholesterols are inadequately treated now, why aren't you gearing the OTC population to that population?

Why do you even need a physician involved?

If you're able to explain some benefit to this population that has less of a risk, why can't you do that on a label for people that have a greater risk and, you know, develop a paradigm for treating them? Why are you limiting it to that?

DR. COHEN: Theoretically that could be done, but I think that's a group that we would say really has a higher risk by definition of whatever we want it stated as, a diabetic, let's say, or somebody with heart disease.

Those patients should be clearly within the confined medical care system, and so with the warning says, "Do not use this product if you have that high risk" whatever it is, diabetes, heart disease.

Then, in fact, hopefully you will not purchase this product or you will discuss the potential purpose of it with your provider.

DR. GANLEY: But why? If physicians aren't adequately treating it now, why shouldn't the message get out there to the people most affected?

DR. COHEN: Well, it gets to the one size fits all question. Okay? And the definition of 200 to 240, I think we can get the majority of them below

the ideal level with low dose therapy that might be proposed, whereas if you're saying the levels are much higher, then you can't really get there very often in the face of low dose therapy.

DR. GANLEY: But I guess if you go along with that philosophy, then someone that would get from 240 to 230 would obtain some benefit. Well, wouldn't it be better to get them under 200? It's the same titration type argument.

DR. COHEN: I agree.

DR. GANLEY: So why? You know, that goes back to the question. If you're going to treat this population, why are you limiting it to a population with the lowest risk?

DR. COHEN: This is the target population really, and it's not limited necessary, and you could purchase it if it were available if you are that high risk individual, and in my opinion, you would do some benefit even though you may not get down to the levels that NCEP defines as normal. You would, in fact, get your levels, let us say, 15 to 20 percent lower, and that I think would translate into a lower risk at least on a population basis.

DR. DeLAP: Dr. Jenkins.

DR. JENKINS: I guess following up on what

Dr. Ganley just asked you about, I'm confused here about the OTCness of this product because you see to be suggesting that the only thing that would change really optimally in the care setting is that patients would buy this over the counter, but they would still see their physician for their risk assessment. They would still see their physician for their follow-up. So the only thing you're proposing to change is how they buy the drug; is that correct?

DR. COHEN: Basically so. We would like to have this as an option.

DR. JENKINS: That's an atypical OTC drug. I mean there are some drugs out there now that say if you've been previously diagnosed by a physician and have used this drug before, you can use it again without seeing your physician or consult your physician before using the drug.

But one that simply changes the marketing from prescription to OTC, but still says you need the physician to use it optimally, that would be a very atypical product.

DR. COHEN: Well, I'm not familiar with everything that's available OTC, but it may fall into what we've got, an atypical problem here, and that problem is a mass killer of coronary disease, and

we've got to address it in ways that aren't being met at the present time, and that includes bringing people into the system who may not be currently treated, and that as I see it is really a very important step in terms of the availability OTC to solve this problem.

We've got a huge problem. Together we've got to do this. I heard yesterday a plea to the FDA panel and the agency as a whole to approach this as an open mind with regard to what can be done and what should be done, with the important safeguard of safety, safety, safety and efficacy, and then looking at the potential in terms of benefit-risk ratio.

DR. DeLAP: Yes, Dr. Temple.

DR. TEMPLE: I thought you were actually saying that while you think optimal therapy would involve continued participation of the physician, you think things would be better off even if that didn't occur, even whether it's a high risk person, moderate risk person. You still think that you'd be better off even if you didn't behave optimally. Isn't that --

DR. COHEN: Bob, if you moved the whole distribution of the cholesterol to the left, it would really make things better.

DR. TEMPLE: Well --

DR. COHEN: So if the population were

taking it as a whole or if people were taking it inadvertently, then I think that we'd be better off on the average, yes.

DR. TEMPLE: I'm trying to follow up on Dr. Jenkins' question. Your answer was that, yes, you really did want it to be part of the usual system.

DR. COHEN: Yes, absolutely.

DR. TEMPLE: So he had asked quite properly, well, what's changed. I thought you accepted his answer too quickly because I really think you mean that even if they don't do it right, they'd be better off. I mean, I think that's sort of the fundamental argument.

DR. COHEN: I think that's what I said or at least I hope that's what I said. I mean, the risk of doing it wrong is relatively small with regard to the benefit, and that's what we need to assure ourselves of in the long run.

DR. DeLAP: Okay. Well, we need to move on.

DR. COHEN: Thank you for all the questions.

DR. DeLAP: And I'm sure we'll continue to have some discussion on these same points with the next speakers. Thank you.

We'll move then to Dr. Jeffrey Anderson, University of Utah.

DR. ANDERSON: Members of FDA, ladies and gentlemen, good morning. I thank you for the opportunity to address the potential of OTC availability of cholesterol lowering medications, and I also wish to address the committee as an advocate for the review of this new application.

I do so as a physician with a long history of interest in broad research and clinical experience in pharmaceutical therapies. I also have been exposed to industry's role in drug development and respect the value of ethical pharmaceuticals, and I understand the special responsibilities of regulatory agencies, having served on the FDA's Cardiorenal Advisory Committee.

I do wish to disclose that my participation today was suggested by Merck & Company, and they are sponsoring my trip. However, the views I express are my own.

As Dr. Cohen has very nicely described, cardiovascular disease is our leading cause of death and disability. Almost a million Americans die of it each year. Perhaps surprisingly slightly more women than men are affected, although women develop it about

ten years later.

Coronary heart disease of heart diseases is the single most important cause of death, claiming almost a half million lives annually. Over a million suffer myocardial infarction or heart attack annually, and 12 million are alive with a history of a heart attack or angina pectoris, perhaps an equal number with undiagnosed disease.

Heart disease also is our leading cause of disability. Medicare spends $11 billion each year on coronary heart disease.

As we've already heard, high blood cholesterol is a major and well established risk factor for coronary heart disease, and even average levels of cholesterol and its low density or bad lipoprotein fraction are associated with increased risk when accompanied by low levels of high density or so-called good lipoprotein cholesterol.

I would also like to emphasize that almost 60 percent of the U.S. population, the majority, have undesirable levels of total cholesterol, LDL and HDL, or clinical heart disease, and half of these, about 30 percent, have cholesterol levels in the range of 200 to 240 milligrams per deciliter, a range that is average or only slightly elevated, and I count myself

in that category, by the way.

Yet the Framingham study suggests that at least a third of all coronary events occur in this range. These are people who are not eligible for treatment by their physicians under current guidelines.

Full recognition of the importance of lowering serum cholesterol for risk reduction has been long in coming. I recall my excitement as a first year Harvard medical student reading a landmark study in the New England Journal of Medicine in 1967 by Drs. Frederickson, Levy and Lees describing how fats are transported and lipoproteins and classifying the hyperlipoproteinemias into five distinct types.

I pursued my interest at that time with a student fellowship in their laboratories and clinics as a third year medical student in 1971 and shared in the excitement of those years.

Well, here we are, almost three decades later. Unfortunately the early experience with lipid lowering was not particularly promising. Available drugs were only modestly effective, poorly tolerated, and some actually increased the risk of adverse events, for example D-thyroxin or estrogen therapy in men.

Diet also fell short. Adherence was difficult, and inherited metabolic factors were found to be more important then diet in determining cholesterol levels.

I recall a particularly cynical article in the New England Journal of Medicine in 1977 entitled "Diet Heart: End of an Era." So cholesterol lowering at that point had hit rock bottom.

But then in the 1980s a new approach emerged, a blockade of cholesterol synthesis at the key step of HMG-CoA reductase, and drugs that inhibit this synthetic enzyme became known as statins.

I was an investigator in EXCEL, a major study published in 1991 of the first marketed statin, Lovastatin, in 8,000 patients. The excellent tolerance, safety, and cholesterol lowering ability of Lovastatin were impressive, but what remained to be shown was whether this reduction could, in fact, translate into a reduction in adverse events, heart attacks, and improved survival.

This beneficial potential of the statins has now been well demonstrated in a series of singularly successful and self-reinforcing studies published in just the last six years. These began with populations at highest secondary risk and then

proceeded and concluded with those at average to slightly elevated to primary risk.

In each of these studies the benefit of statins was shown. The first of these, the Scandinavian Simvastatin survival study, published in 1994, tested Simvastatin in patients after a myocardial infarction. SSSS demonstrates substantial survival benefits in these patients who had also high cholesterol levels.

Deaths were reduced by 30 percent, coronary deaths 42 percent, any coronary event 34 percent.

The care and lipid trials with Pravastatin extended benefits to the majority of patients after MI and many with average cholesterol levels.

The West of Scotland study, or WOSCOPS, next showed that statin therapy could prevent a first heart attack in subjects with very high levels of cholesterol.

And most recently, in 1998, the Air Force, Texas coronary atherosclerosis prevention study, extended the demonstration of benefit in primary prevention to those with average cholesterol levels and no evident heart disease.

Among 6,600 participants, Lovastatin

reduced fatal and non-fatal heart attacks, unstable angina, and sudden death by 37 percent. It also indicated beneficial potential and safety in subjects resembling those who would be candidates for OTC statin therapy.

Well, given that background, what then is the next step in primary risk reduction through cholesterol lowering? I believe the next logical step is to review and, if appropriate, then approve the statins for appropriate OTC use.

Today the public is better informed and more interested than ever in personal risk factor reduction. At the same time and sadly, funding for programs within our traditional health care system is diminishing. There is a growing gap between primary preventive efforts and public concern about risk factors.

The consumer already has moved to fill this gap, even if ill advised, through self-medication with so-called nutriceuticals. I'm told that 65 million Americans or one-quarter of all adults are concerned about their cholesterol levels, and of these one-half already use a nutriceutical, such as Vitamin E, garlic, niacin, and herbal preparation, for example.

Though often relatively ineffective in cholesterol lowering and largely unsupported by randomized trials, these products form the fastest growing segment of the health product market, with $12 billion spent last year.

Patients in my own practice regularly list self-selected health supplements in their medical histories. One of these, red yeast rice, contains Lovastatin in doses that approximately the proposed OTC dose and is available to the public and has generated a good deal of interest.

We in the health care community should recognize this entrenched and growth public health movement towards self-medication for risk reduction and respond constructively.

In considering OTC statins for primary prevention, four questions come to mind. First, what is the advantage of this approach?

These products derive from good manufacturing processes, insuring reliable dosing and purity, are backed by clinical trials, should be and would be, I hope, marketed in a regulated and in educational environment, are safe. For example, the adverse effect rate, event rate, with a dose of 20 milligrams of Lovastatin, twice the proposed OTC dose,

is no greater than placebo, and a further public health advantage of expanded statin use is that each individual who lowers his or her risk contributes to the general health of our nation.

Second, why should we move ahead now? Now is the appropriate time because of the convergence of evidence, feasibility and interest. Evidence for benefit and safety of long-term statins in this average to slightly elevated cholesterol primary prevention population is now available from the AFCAPS/TexCAPS study. Easy, reliable, automated approaches to cholesterol testing to guide therapy also are now available directly to the public.

Finally, the public already has shown substantial interest in pursuing OTC approaches to coronary risk reduction, as I've mentioned.

Third, what should be the target population? The greatest unmet need and demand lies in the population with average to mildly elevated cholesterol levels. These levels of 200 to 240 generally do not meet guidelines for drug therapy, although that is under review, as we've heard, and yet over a third of total coronary events occur in this range.

There is now evidence for benefit and

safety of statins in this cohort. So the question is: why should we limit the choice and access of interested responsible individuals within this group to unproven, relatively unregulated nutriceuticals?

And finally, fourth, how will this affect the physician-patient relationship? The answer is, I believe and would hope, that it should enhance it. The patient encounter with an ethically formulated, marketed product can educate and triage. Patients whose cholesterol levels place them at high risk and those with concomitant diseases or interacting medications would be instructed not to self-medicate, but to see their physicians.

A proper OTC initiative would also increase awareness of the use of drug therapy as an adjunct to diet and exercise in a primary prevention and open a new dialogue among physicians, other health care providers, and the public.

This population targeted for OTC use otherwise is unlikely to be treated or covered by current insurance plans.

Finally, the educational encounter could reassure those at lowest risk who should continue with healthy life styles.

In conclusion, I believe that OTC

cholesterol lowering with low dose statins is a rational treatment option that health care consumers should have the reasonable right to choose. I urge the FDA to consider and carefully review applications for OTC statin use by subjects at moderate coronary risk who choose to practice improved primary prevention.

Thank you for your attention.

DR. DeLAP: Thank you.

Dr. Jenkins.

DR. JENKINS: Yeah, thanks for that.

I'd like to follow up on a question that Dr. Temple asked Dr. Cohen earlier, and that's what's the evidence of benefit in this patient population that you're referring to for your target population. You're targeting total cholesterol, 200 to 240, and you're citing primarily the AFCAPS trial. Other than the epidemiologic data, that's the primary clinical trial that may show some benefit from a cardiovascular standpoint for this group.

And yet that study specifically recruited people with low HDL cholesterol. So do you think that HDL cholesterol should be part of the OTC paradigm? Should we only be targeting patients in this group who have low HDL cholesterol? And if so, how would you

accomplish that in the OTC setting?

DR. ANDERSON: Well, I think that's a very good question, and I think that one could go either way, choose simplicity. That is, the majority in the range of 200 to 240, in fact, would meet those guidelines or, in fact, measure HDL cholesterol which would require a more sophisticated approach, but can be done with current technology. It can measure HDL.

In my own practice, I prefer to also look at HDL. I would just add though that the entry criteria for AFCAPS/TexCAPS with respect to HDL were not very strict. I believe it was less than 50, which is very common.

So I think that that would deserve more discussion and should have full review, that question, simplicity versus a more exact stratification and triage.

DR. DeLAP: Dr. Temple.

DR. TEMPLE: Not to name names, but some statins have problems with interactions, and in the OTC setting presumably strict avoidance of antifungal agents and things like that might be harder to communicate than others.

Is that a worry? How worried would you be at the low doses that you're talking about?

DR. ANDERSON: Well, I think that that's important and should be obviously stressed in any approach. I mean I think that this should be different than perhaps some other OTC medication. It should be like joining a program where there's adequate educational material and there's interaction with pharmacists and with physicians and other health care personnel along the way.

But I think at this does, at least my read is that these are safe medications. Lovastatin, for example, has been out there for 13 years, and there is a wide margin of safety in terms of the dose that can be taken and tolerated, and what would be given in this program.

So that should clearly be addressed. I agree with Dr. Cohen that safety is a key issue. I do believe it can be addressed.

DR. MURPHY: Let me follow up on that. Is it fair that you're saying that you believe that the population that wants to self-medicate will continue to seek other approaches, and that that risk is higher than the proposed OTC for the statins that you're -- for the reasons that you've stated about manufacturing, et cetera? But is that sort of a summary of what you're saying?

DR. ANDERSON: By other approaches, nutriceuticals and so on?

DR. MURPHY: Right.

DR. ANDERSON: Well, I think the group that is into risk reduction, is into self-medication will, my view is, will be better served more safely, more reliably by low dose statins which, as I mentioned, actually can be taken in a nutriceutical formulation right now without any assurance of safety, of dosing reliability, or of purity.

Hopefully though this will also encourage people who otherwise would not take anything because of those concerns into doing that because they would be assured that the product they're taking has been tested, is pure, and that they can take a reliable dose, and also would have access to educational materials and interaction with other health care personnel in guiding treatment of their high cholesterols.

So I think it would expand beyond those who are currently in that setting, but certainly would deal more effectively with the group, the large group, the growing group, that is taking a number of products OTC.

DR. DeLAP: Mr. Campbell.

MR. CAMPBELL: Are you suggesting that such products should be behind the pharmacy for pharmacy, that you had to go to a pharmacist to use them, or is it purely over the counter? Because you mentioned educational materials.

DR. ANDERSON: I really didn't come prepared to propose a specific guideline. I think there needs to be more interaction certainly in terms of educational materials and other programs perhaps with a pharmacist than with other OTC products because it is a chronic product, but I think that that should be a focus of discussion.

I have seen a number of proposals, some of which included that format; others have not, that I think are reasonable to consider.

DR. DeLAP: Dr. Jenkins.

DR. JENKINS: I'd like to get your views also on the issue of compliance. We know that this would be in many cases lifelong therapy, and now you're targeting people who have a lower risk of cardiovascular disease and, therefore, may need to take the drug five, ten, 15, 20 years to get an individual benefit to that patient.

We know that in the prescription setting with doctors involved and nurses involved, compliance

with these chronic therapies is very, very pool. So what's your thoughts about how can we actually derive a benefit for the individual patient given compliance in the OTC setting for a chronic medication like that? Do you think that's actually going to happen?

DR. ANDERSON: Well, the first thing I would say is that the medications are incredibly well tolerated. So I don't think that adverse effects is going to be a factor in terms of limiting compliance. I think it's a matter of individual motivation and choice, and the people that I think will self-select to take this chronically are those who are motivated, who really are worried about risk factors. We'll follow them along and will track them, who also exercise, will be on a good diet, and so forth.

So it's true that some will start out and fall by the wayside, as they lose motivation, but it's for those who really want to affect their primary risk who will be ignored by their current physicians in their current environment or don't feel that it's appropriate to use up health care dollars for that that will take it long term and will benefit.

DR. JENKINS: As a follow-up to that, do you have any concerns about patients who might with this available over the counter misuse it so that they

can continue to eat their unhealthy diet, not to name names.

(Laughter.)

DR. JENKINS: And continue not to exercise appropriately? Do you see that as a concern and how much of a concern?

DR. ANDERSON: I don't have data on that. I think that likely those will be the ones who will be in for the short term and try it for a few months and then go back to their previous lifestyles, but this should be an adjunct along with other measures, although I must say of the three thing, it's probably going to have the greatest impact on LDL.

You know, a lot of people get discouraged because exercise doesn't do much. They try diets and it only works partly.

DR. DeLAP: It's hard to get a question in edgewise here at this point. I'd like to ask one question, and I think I know what you'd say to this, but I just want to be sure. Clearly, as we've looked at different kinds of cholesterol lowering agents over the years, not all cholesterol lowering is created equal. Some products may lower cholesterol, but not give you the same benefit, say, as the statins seem to be giving.

Now, within the class of statins, given how difficult it is to do real outcome studies and confirm what the treatment outcomes are, within the class of the statins, do you think that we should be regarding them as a class in the sense that if you have a drug in that class and it provides a certain level of cholesterol lowering, then we know what that translates to in terms of benefit based on a study that was actually done with a different drug in that class?

DR. ANDERSON: This is a very difficult question to answer, you know. Sort of speaking as a former panel member, regulator, obviously one is most confident using the specific agent in the specific dose in the specific population, and there one can, you know, pretty much rely on the result, and there's less confidence the further one steps away in terms of chemicals, doses, and population, and I think the same would apply here.

You know, I personally believe that among at least the two or three statins that had been used in broad clinical trials, the data are quite consistent, and I think that there certainly is a class effect, but there certainly are ancillary drug properties that may add or detract from that effect.

I don't think all statins are exactly equal, and other have editorialized about this.

So I think this will be a difficult question to deal with. It should be carefully and thoroughly reviewed, but I don't know that I have an answer to give you today.

DR. DeLAP: Dr. Jenkins.

DR. JENKINS: I just wanted to clarify one point. In reading through your statement, there's a lot of references to public health and societal benefits. Can you clarify is your enthusiasm for the OTC availability of these products directed towards the individual patients who would use them or are you more enthusiastic from an overall societal lowering of cardiovascular risk and mortality?

DR. ANDERSON: Well, I think both of them certainly add to the enthusiasm. As I mentioned, there's sort of a convergence of win-wins here that suggest that this is a good step to take. I suspect that my enthusiasm would be almost equally applied to both of those with particular emphasis on individual choice though in this particular situation. I think later, as we get more information as we perhaps can fund more therapies for broader groups of people that it might have greater impact on public health.

DR. DeLAP: Dave Fox.

MR. FOX: Are there any comparisons that can be drawn between the way we have regulated low dose aspirin, which is now -- I mean the entity is available over the counter, but the indication for stroke and recurrent heart attack, second heart attack is supposed to be done through intervention of the physician, by professional use only.

I'm just wondering if there's any comparison that can be drawn there.

DR. ANDERSON: I'm not sure how far we can take that. Aspirin obviously is very easy to get any way. So this would be a little different in this case, and by the way, I think the evidence for primary prevention there is still controversial. That is, it does reduce heart attacks, but there's a concern that it doesn't offset morality as well.

So I personally recommend aspirin for secondary prevention on a routine basis, but not necessarily for primary prevention. So I think that there probably are some limited comparisons, that is, it's a chronically used medication. You have to be concerned about safety, as well as efficacy, but there are also some major differences.

DR. DeLAP: I think we --

MR. FOX: Differences in the sense that there you think on balance you do need the intervention of a physician, and with the cholesterol lowering on balance you think the risk-benefit points the other way. You could tolerate not having the necessary step of a physician intervening.

DR. ANDERSON: Well, I think I'm not sure if that's exactly the difference that I was thinking of specifically. Certainly interaction with health care personnel, physicians and pharmacists and other providers, I think is to be recommended in all of these settings, and certainly that should be encouraged in this setting as well, but I think physicians, we simply don't have the manpower or potential within our current medical care system to handle 60 percent of Americans in this system, and so that's the limitation.

DR. DeLAP: Well, I think we could continue this discussion for quite a while. Dr. Ganley, do you have something very quick? Because I think we will need to move on.

DR. GANLEY: Yeah. I just want to provide or ask the same question I asked Dr. Cohen about, you know, it's obvious at higher cholesterol levels in people with previous risk, they derive the most

benefit, which would be easy to quantitate on a label. Yet you don't want to include that population as the OTC population. I'm not sure why that is.

DR. ANDERSON: Well, I think I'd have to sort of reiterate Dr. Cohen's response, and that is -- and it does seem pyridoxic clearly on reflection -- is that those patients in the highest risk need to, in general be on higher doses. They need to be titrated. There is greater need, therefore, to be concerned about side effects which are dose related with, for example, liver function abnormalities, myopathies, and so forth, and that's the reason to triage them into the medical system.

So what we should do is try to get those patients into the medical system, and that's the win-win in terms of physician-patient relationship, is to use that as the first approach.

Now, obviously they can take it out of label or use it out of label, if you will, and they'll probably benefit more by it than if they didn't do anything. So I think that's the other side of it.

DR. DeLAP: Okay. Well, thank you very much.

I think at this point in time we're way overdue for a break, and I think we'll have a 15-

minute break, but we will start precisely 15 minutes from now because we're a little behind.

(Whereupon, the foregoing matter went off the record at 11:13 a.m. and went back on the record at 11:32 a.m.)

DR. DeLAP: Our next speaker is Dr. Edward Frohlich, representing the American College of Cardiology.

Dr. Frohlich.

DR. FROHLICH: Thank you very much, and I apologize that I have come out of sequence if those of you have the score cards are keeping score, but my name is Dr. Edward Frohlich, and I'm pleased to speak today on behalf of the American College of Cardiology, or as I will refer to it, the ACC.

I'm a fellow of the ACC, as well as a member and Master of the American College of Physicians. I've also served as a member on the Board of Trustees of ACC, and I might say parenthetically on the first Cardiovascular Renal Advisory Committee of this group.

I am currently the Alton Ochsner Distinguished Scientist of the Alton Ochsner Medical Foundation and the Ochsner Clinic in New Orleans, and I'm Editor-in-Chief of Hypertension, an official

scientific journal of the American Heart Association.

The ACC appreciates this opportunity to offer its comments regarding the Food and Drug Administration's approach to regulating over-the-counter or OTC drug products. The ACC is a 25,000 member nonprofit professional medical society and teaching institution that represents over 90 percent of the nation's cardiovascular physicians.

Our interest in the FDA's regulation of OTC drug products grows out of a primary responsibility as cardiovascular physicians to insure that patients have the best care available to them, care that is safe, effective, appropriate, and comprehensive.

And our testimony today is provided with that responsibility clearly in our minds. We are advocates for good drug therapy because we know that when appropriately utilized, they can substantially improve patient outcomes.

Within that framework we propose guidelines for the FDA to consider when evaluating applications for OTC status. We find that the FDA's current regulatory approach insures that "consumers have easy access to certain drugs that can be used safely for conditions that consumers can self-treat

without the help of health care practitioners," and is the correct approach to regulating OTC drug products.

The ACC has developed a set of guidelines that we believe are appropriate for FDA application and are all cardiovascular OTC drug products globally as considered today. We believe that our guidelines are fully consistent with the FDA's regulations, and the following summarizes areas of general agreement between the ACC and the FDA.

First, low side effect profile. Like the FDA's regulations, we believe that drugs made available for OTC use should have a, quote, low incidence of side effects. We add that where side effects exist in an OTC drug, they should be of the type which can be monitored without physician assistance or testing.

For example, nonsteroidal anti-inflammatory drugs typically can cause stomach upset prior to gastric ulceration.

We further believe that side effects which can only be detected by laboratory tests or physician monitoring compromise consumer safety by going undetected until they become severe enough or life threatening. Thus, drugs with such side effects should not be available OTC.

Second, low potential for harm due to abuse. The FDA regulations state that an OTC drug should have "a low potential for harm which may result from abuse under conditions of widespread availability." We agree with that potential for harm if abused and should below.

We would add, however, that drugs which have a great potential for abuse should not be available OTC, even if the harm from abuse is not great. Such a drug would not be a good OTC candidate because it would not be used according to "adequate directions for use and warnings against unsafe use," and hence would not provide the type of relief claimed.

As an example of an abuse of an OTC drug might be for fraudulent purposes. It is conceivable that certain drugs may be taken over a short duration to achieve a clinical endpoint in order to mask a clinical condition. For example, the individual where FAA or Federal Aviation Administration licensure or insurance approval is required.

Anti-hypertensive agents, for example, may lower blood pressure rapidly, allowing a person with hypertension to appear normotensive for an FAA exam or an insurance exam or even pre-employment exam. Such

fraud has cost or can cost the immediate incident, and these costs may be also with the higher insurance premiums for all or a danger to public safety in the case of the pilot who is not on regular treatment program yet passes an examination.

Third, clinically significant relief. FDA's regulations define "effectiveness" as "a reasonable expectation that in a significant portion of the target population, the pharmacological effect of the drug will provide clinically significant relief of the type claimed."

Since OTC drugs are usually available in the lowest possible therapeutic dose, those doses which are subtherapeutic should not be made for OTC use. This is especially true for drugs that do not produce symptoms, or if a drug's claimed relief requires laboratory tests or some other technical intervention, consumers may believe that they are relieved when, in fact, they are not.

Thus, the following is an important guideline that the American College of Cardiology would add to FDA regulations, and that is the existence of symptoms.

The prescription of drugs which the FDA has thus far changed to OTC drug status are used to

relieve consumers' symptoms. For example, the nonsteroidal anti-inflammatory drugs alleviate pain, and when the consumer uses an over-the-counter NSAID, he or she knows when it's effective on the basis of the pain that is relieved.

Likewise, H2 blockers are used to relieve heartburn, and their effectiveness is known to the consumer based on symptom relief.

The ACC believes that the relief of symptoms should be an important requirement for OTC product. If, on the other hand, a currently available OTC drug does not relieve a symptom, the consumer is more likely to seek the advice of a health care professional for providing the relief.

However, if relief requires a laboratory test, the consumer does not know whether he or she, in fact, are relieved. This is especially important for cardiovascular drugs which often can treat conditions which no associated symptoms with which a consumer can assess the drug's efficacy.

The risk of subtherapeutic dosage or suboptimal therapeutic endpoints is increased when a drug requires monitoring to assess effectiveness. High risk consumers and those with established disease are particularly vulnerable, and we believe that the

management of these patients should always be supervised by a physician.

It is, therefore, of vital importance that if drugs used for treating such silent conditions are made available OTC, important information must be provided regarding all risk factors and their management. We propose that medical specialty societies participate in the preparation of guidelines for patients who would use OTC drugs. Such guidelines are appropriately developed by physicians with input from patients and can include information on when the taking of an OTC drug may or may not be benefit under supervision of the physician.

Risks will increase if OTC drugs are taken without appropriate monitoring and consumer access may actually be hampered when drugs that are available OTC are no longer covered by health plans.

We also believe that drugs that do not relieve symptoms but instead require some other intervention to assist the effectiveness do not qualify for OTC basis based on the Congress' mandate that drugs requiring "collateral measures necessary to their use" be available by prescription only. Laboratory determinations and professional supervision for follow-up constitutes such "collateral measures,"

making drugs requiring such monitoring unacceptable for OTC use.

So in conclusion, we understand that the FDA is considering changing its criteria for OTC status and considering drugs which are to treat silent conditions, as well as conditions which are chronic and often multi-factorial in nature.

We understand that OTC status may increase access to certain drugs which are safe and, therefore, reach populations which have not benefitted heretofore. We applaud such efforts to increase such access to appropriate drugs and therapies.

However, we also believe that the FDA must carefully consider OTC status for drugs which treat those conditions described above. Coronary artery disease is an excellent example of a chronic disease that is multi-factorial and often without symptoms until well advanced. Physicians treating such patients address all risk factors and institute and monitor therapies beyond pharmacological interventions.

Physicians advise on life style changes, including diets, smoking, exercise, other interventions, as well as monitoring the responses to such therapies that we talked about. In such cases,

such lifestyle changes eliminate the need for pharmacological therapy and have benefits beyond the specific condition where they're instituted.

These collateral benefits should also be taken into account when an OTC switch is considered for drugs treating conditions such as these.

The ACC neither recommends nor opposes OTC status for any particular drug with this testimony. We believe that such switches should be based on sound evidence that benefit consumers. We strongly believe that consumer education is of paramount importance with any new drug class that becomes available OTC, and we look forward to working further with the FTC as it continues to review its regulatory framework for over-the-counter drugs.

And I should be happy to answer any questions at this time, sir.

DR. DeLAP: Thank you, Dr. Frohlich.

Questions? Dr. Cantilena.

DR. CANTILENA: Yeah, just a question about your comment on the guidelines for the patients. Can you tell me what you're referring to in terms of are the guidelines going to be something that would be for a specific, you know, product or, you know, disease?

And also, how would those guidelines be distributed, you know, like in the actual package or at the physician's office or in the pharmacy?

DR. FROHLICH: It's a good question. The guidelines are already available by FDA. We have gone through each and every guideline step by step as presented by the FDA, but we added the one issue as it concerns symptoms because we felt this was important, but it is well known, and this is what we based our response to you and your committee today, based on those guidelines that exist adding one additional caveat.

DR. CANTILENA: I was actually, you know, referring to the guidelines for patients who would use over-the-counter drugs.

DR. FROHLICH: This is what I'm referring to, yes, sir.

DR. CANTILENA: Okay, okay. I misunderstood what you were saying before. Thank you.

MR. FOX: Several of the speakers have noted prominently the presence and availability, popularity of dietary supplements, and patients or consumers are seeking those out. To what extent, if at all, do you think that affects the paradigm when looking at Rx versus OTC, the extent to which we

should as a policy matter start to consider the availability of dietary supplements?

DR. FROHLICH: Well, let me speak from my point of view as a practicing physician and not as an individual representing ACC. We haven't made any position on nutriceuticals or the like.

It does confuse the problem. There have been recent reviews in journals, such as the New England Journal, in the past month or two that talks about the number of nutriceuticals that are available and how they can interfere by drug-drug interactions and the potential.

Because FDA does not have the mandate to go over that each of these improve efficacy, it's very difficult for the FDA to follow this. This is an issue that is of great concern when we know a number of patients with cardiovascular disease, for example, are taking anticoagulants, and there are a number of nutriceuticals that can affect prothrombin times and so forth.

So I think this is an important issue that you're going to have to face, Bob, with your group and to see how this can be addressed as you go into the consideration of a wide spectrum of other drugs. We are looking more globally at all cardiovascular drugs

than any one single class of agents.

DR. DeLAP: Yes, Dr. Woodcock.

DR. WOODCOCK: Yes. You make the point that asymptomatic conditions would be more difficult for a consumer to recognize and treat, and you make the point that the ideal clinician intervention would be counseling on diet, exercise, cessation of smoking, and reduction of risk factors, as well as potential pharmacologic interventions.

One of the --

DR. FROHLICH: In addition.

DR. WOODCOCK: Pardon me?

DR. FROHLICH: In addition to.

DR. WOODCOCK: In addition, yeah.

One of the issues that we're discussing, however, is the fact that that is widely failing to happen even in the clinician interaction with patients, and that is widely acknowledged and documented.

DR. FROHLICH: I missed what your "it" is.

DR. WOODCOCK: For example, there's an article in the Washington Post yesterday or recently about and it included the fact that very few clinicians are counseling smoking cessation. So the reality is this isn't happening. That's why we're

having this discussion, I think, is that patients are not receiving or consumers are not receiving the proper counseling advice and even consideration of pharmacologic interventions even though they may be attending a physician.

DR. FROHLICH: You raise a very important point. I, again, have to speak as an individual. I personally believe that there has been a tremendous impact on consumer education on this. Not enough people have stopped smoking. Not enough people are losing weight in this country, for example. We don't have very good behavioral modification techniques available, as you know, to us medically.

Nevertheless, if you look at the decrease in smoking in this country, we have come a long way, baby, as they say in their ads for women who smoke.

I think, for example, we need to apply better and continuous educational methods. Coming from an institution that started the relationship of smoking and lung cancer advised by Alton Ochsner many years ago, I can tell you that we have, in fact, decreased the amount of smokers.

We need to do better. The number of smokers and the number of people smoking in this room is markedly different than it would have been 25 years

ago, 30 years ago. So we have done this, and physicians must do this with their patients. There's no excuse not to. It's just a question of continuous education, and you know the public media is such that they have a disease of the year that grabs them.

Back in the '70s we had hypertension, which was very exciting. Then in the '80s we had cholesterols. Now it's maybe breast screening and cancer, but the issues here have to be -- all of them have to be -- addressed continuously, and I couldn't agree with you more.

DR. DeLAP: Yes, Dr. Temple.

DR. TEMPLE: Ed, you draw a sort of bright line between treating symptoms and treating signs, I guess you could say, and one of the reasons is that a patient can't assess whether his sign has improved without some external help.

However, in two conspicuous areas, cholesterol and blood pressure, you can go to your Giant Supermarket and get your latest blood pressure. I don't know how accurate those are, but you can do it, and there are or will be simple tests of cholesterol available.

So a person who was taking an over-the-counter drug in order to modify those signs would, if

they were interested in the first place, be able to see how they were doing, if they bothered. Does that affect your view of the bright line?

The other I saw had the same question. I thought what David Fox was asking was -- that's the question over there -- was whether the fact that people are treating their blood pressure with garlic makes you more inclined to think that maybe they should have something that would work.

(Laughter.)

DR. FROHLICH: Well, again, I agree with you, and as you know, the announcement of this meeting that caught the attention of the American College of Cardiology was to address more globally all of the cardiovascular drug therapies and not any one specific. I know you're going to be talking at least next month about the issue of cholesterol. So, again, I would have to be thrown to my own point of view because our leadership has not addressed any one class of drugs.

But, yes, I think there has to be monitoring by the patient reliably, and as you know, in the hypertension area patients have been taking home blood pressures for many years and doing a good job of this, but not necessarily people taking home

blood pressures and treating themselves with effective anti-hypertensive therapy. This has to be worked out very clearly, particularly with a much more potentially dangerous class of drugs.

The statins is another issue, and again, I have been searching my mind how patients can do this. Perhaps they can work out with health care providers copies of laboratory tests that can be sent to their physician and they can continue on. Perhaps the companies might even provide tear-offs from labels that after five purchases of four or five months of treatment they can have a copy of a laboratory test done when they submit five labels for a laboratory examination. A copy would go to the patient, a copy to the physician.

We have to be just as innovative in this look as you are in looking at over-the-counter innovation, and i think both of these have to mesh together and still follow your mandate from Congress.

DR. DeLAP: Well, I think that that's --

DR. FROHLICH: Have I answered your question, Bob?

DR. TEMPLE: Well, except about whether you're influenced by the fact that people are self-treating these very things. I mean you talked about

the potential for interactions, which is certainly a legitimate worry. I think the question was whether the world as we know it, in which people are using a variety of substances to treat these very things, should influence us.

DR. FROHLICH: Yeah. My personal experience as a person treating hypertensive patients now for 40 years, I don't have the problem necessarily of the nutriceuticals and blood pressure. They soon become available is not very effective.

On the other hand, I don't know what happens with these other drugs. I have not seen enough patients that will treat themselves with statins, although, you know, statins are available outside the United States. I don't know how many people are using them over the counter.

DR. DeLAP: Okay. Thank you very much.

DR. FROHLICH: Thank you.

DR. DeLAP: And I apologize for how far behind we're getting here to the upcoming speakers, but I think this discussion is very useful to the agency.

Our next speaker is Lorie Rice from the UCSF School of Pharmacy.

MS. RICE: Thank you for the opportunity

to speak with you today.

My name is Lorie Rice, and I'm here to convey my perspective of key issues in the consideration of cholesterol lowering drugs for OTC status.

It's been a while since the last time I participated in an FDA hearing, and I can tell you now it's much easier to participate on the other side of the microphone.

Before I begin, I want to disclose that I serve as a consultant to Bristol Myers Squibb. My full-time job is the Associate Dean of External Affairs and assistant clinical professor at the University of California, San Francisco, School of Pharmacy. I teach pharmacy law and ethics.

My comments today, however, are my own, neither those of Bristol Myers Squibb, nor UCSF.

I served as a consumer representative on the initial NDAC for four years. It was both an honor and a marvelous learning experience. Representing consumer interests, however, was not a new experience for me. In California, I served as the Executive Officer of the State Board of Pharmacy for seven years, and then I served as a consumer representative on the State Board of Behavioral Sciences.

In May I was appointed by the governor to serve on the State Medical Board, again, as a consumer representative. I take these responsibilities with utmost seriousness.

This is an excellent time to be a consumer representative. Consumers themselves are becoming more vocal and more engaged, and you've heard this several times this morning.

This is particularly true in the area of health care or self-care. The reasons for consumer involvements actually come as no surprise. First, the rise of managed care has, to a large extent, depersonalized health care and made it challenging for patients to get quick responses to their health care needs.

Also, every day consumers find more products and more information at their fingertips or at the click of their mouse. Many adults rely on multiple sources for their health information, such as television, magazines, and journals.

The explosive use of the Internet has also provided a readily accessible method of disseminating and retrieving information on everything from herbal cures for hair loss to the molecular structure of antidepressants.

It is no wonder then that consumers are making personal decisions about their health care after gathering information from a variety of sources, some that are reputable and some that are not. The simple fact is that consumers are seizing these opportunities in involvement. All indications are that this trend is unstoppable.

For example, consumer use and interest in alternative medicine is at an all time high. A recent survey in JAMA found that 42 percent of Americans used some form of alternative therapy in 1997 at a cost of nearly $30 billion in unreimbursed expenses.

Between 1990 and 1997, patient visits to primary care physicians remained constant, but their decision to visit complementary and alternative medical practitioners increased by almost 50 percent. This same study noted that almost one in five adults taking prescription medicine also was taking herbal products and/or high dose vitamins.

Consumer pursue these options because they perceive them to be effective and because they are congruent with their values and beliefs about health. In recognition of the consumer demand for information and newer and better ways to participate in their own care, the University of California, San Francisco, has

recently established the Center for Responsible Self-Care.

We are all familiar with and appreciative of the options now afforded the consumer with the many switches over the last several years of prescription drugs to the nonprescription category. When I was a committee member, we evaluated data on safety and efficacy and weighed the benefit-risks for products proposed for OTC status to fill unmet needs. Some of these expanded the definition of OTCness.

As a result, the consumer has been given even more choices for self-care remedies, and these to our benefit have all met the standards required by the FDA.

Today and in July, it will be up to you as well to help consumers as they continue their efforts to help themselves. Along with many others, I look forward to your next meeting when you will have a unique and, indeed, historic opportunity to consider case by case whether an approved cholesterol lowering drug should be made more accessible to an eagerly awaiting consumer population.

During those deliberations, there are specific issues which I would ask you to give your special consideration. These are the points that I

would be thinking about if I were sitting on the other side of the table. I was educated on these points during my tenure on the NDAC, and in fact, the committee's diligent application of these criteria were critical for each and every OTC switch.

First, please remember again that consumers do want to be involved in their own health care, and once they decide to do so, they will begin to try a variety of options. They should be given this chance with products that clearly demonstrate predictable safety and efficacy.

Second, it is imperative that labeling directions provide all the information a consumer needs in order to decide whether the product is appropriate and certainly when and how to initiate and continue administration.

I think that you can feel confident if you are provided with data reflecting a high level of label comprehension in a study of a broad based population.

Third and equally as important, you must be assured that consumers can not only read and understand the directions for use, but they will also follow the label message. This must be illustrated by consumer use trials.

Fourth, especially in cases such as cholesterol lowering drugs, you must be convinced that the doctor-patient dialogue is maintained. A sponsor must present research that provides convincing evidence of minimal interference in that relationship.

Lastly, please be prepared to consider the related and significant benefits that a switch could afford the target population. This was always an important issue for me. Examples include the facilitation of entrance into the health care system, the enhancement of the doctor-patient relationship, and the full array of otherwise unavailable education and support programs which increase health education for the individual and the population at large.

If, upon reflection, a candidate meets these criteria in a data driven matter, you should be persuaded that that drug is, indeed, suitable for OTC availability as a contribution and a complement to their total health care.

Thank you.

DR. DeLAP: Thank you.

Questions?

(No response.)

MS. RICE: Thank you.

DR. DeLAP: Thank you very much.

Our last speaker for this session then is Dr. Bruce Barnett and Mr. Calabio.

DR. BARNETT: Thank you very much for this opportunity, esteemed panel.

Mr. Calabio and I will not stand here together to distract you for the entirety, but I did want you to meet Mr. Calabio.

My name is Bruce Barnett. I'm a physician. I've been a physician for nearly 25 years, and most recently I've become an attorney. I specialize in medically related legal issues.

I have traveled from Los Angeles to be here today, along with John Paul Calabio, to put a face on the difficulties associated with the drugs we're talking about, the statins, so that you have this much data also to consider.

Mr. Calabio is going to sit down right in front so that he's available for questions, and I'll continue now to help bring this data to your attention.

Elnoisa Calabio, the wife, mother, a registered nurse. Her face is in the materials that we presented to you today, along with my CV, by the way, and a written and brief statement about the issues that I want to address.

Mrs. Calabio died as a result of taking a statin, and her death, which occurred in October of 1999, was attributed to statin by the physicians who took care of her, attributed to the statin by an independent medical examiner who looked at her record thereafter.

She started taking the statin in July of 1999 upon the recommendation of her physician. I will repeat this later on, but her cholesterol level at that point, while elevated, did not meet the national guidelines for statin treatment.

This was not the first death from statins that is reported in the literature, nor is it the first death from a particular kind of disease that caused her death. She died from the complication known as interstitial pulmonary fibrosis.

Shortly before her death, Ms. Calabio said to her family members, knowing that it was the drug that made her ill, "Do what you can," she said, "that other people should not have to die as I or become ill from the drug." She died, again, in the fall of 1999.

And, again, in the literature I've attached to the materials I've submitted the kind of death she had experienced had been reported in the literature since 1995.

I expect that the reports in the literature underestimate the side effect which I described. For reasons best known to the FDA, best known to the manufacturers of the drug, and this drug in particular -- and, again, I respect the spirit of these hearings to not name names, but obviously the specific drug involved here will be important. As was said, all statins are not created equal, and I give you the literature, and I give you the information on this drug in the package.

But for reasons best known to the FDA and the drug manufacturer, the deaths and the illnesses from pulmonary complications attributed by scientists to this particular drug do not appear in any of the PDR literature, that is, the material sent to doctors; has not appeared since they've been put together; do not appear today, as you can see in the literature I've given you, and in 1999 or the year 2000 PDR material, nor do they appear in advertisements which are promoted to the public through the Wall Street Journal and others.

The Calabio familiar and I feel the following points are very important. Number one, Mrs. Calabio had an LDL of 158 when she started her treatment with this drug. As we know, the guidelines

say that 158 already is an improvement on the actual target goal for a woman like her with only one risk factor. Her target goal was 160, and at 158 she didn't need the drug.

Mrs. Calabio's cholesterol level, which was admittedly elevated at the time she took it, was what alarmed her doctor, I'm sure, was not check again after a period of exercise and diet, but instead she went right to this drug.

Why did she take it? She took the drug because neither she nor her doctor presumed or believed that any severe harm could come from it. They didn't even see the remote possibility of death.

There is this common misperception also that was played out here. She was started on 40 milligrams of the drug. After all, if 20 milligrams will lower your cholesterol and we want to have the lowest possible cholesterol, then, hey, 40 milligrams must be better.

Number two, the advertising promotions, I think as we see in this case, in many cases, if not universally, have all but drowned out or obliterated the fine print warnings that had been placed by the manufacturers and endorsed by the FDA. Health care professionals far and wide just don't see the statins

as being dangerous or appreciate.

Really, if you think about it scientifically, the profound pharmacologic effect these drugs are having to completely reorient the way our body metabolizes the food substances and creates cholesterol.

Third, this widespread misunderstanding of the potential toxicity, as I've mentioned, leads to a higher than necessary dose, and I believe this is a real risk when we have an OTC consideration. We have a hard enough time controlling how many pills people will take of their aspirin or Advil or Tylenol -- excuse me for naming names -- but we would certainly have the same problem here.

Again, if 20 milligrams helped, 40 milligrams is better.

Fourth, as you'll see from the materials I've given you, Mrs. Calabio did not stop her medication immediately when the very first signs of toxicity appeared in her case. The physicians treating her also did not jump on her case with the extreme level of aggressiveness that would have been merited and possibly would have saved her life, in part, because there's this complacency abounding.

But I think, in part, what we've heard

today and perhaps well grounded in data, but this complacency cannot mean that on an individual case a person can't be fatally affected by this drug, and this complacency has left the doctors unprepared to aggressively treat the side effects. This is, of course, a grave concern to safety.

Number five, and last in my points, is simply this and is why Mr. Calabio, John Paul Calabio, son of Mrs. Calabio, wanted to be here today. As far as that family is concerned, statin was a 100 percent failure. As far as that family is concerned, statin had no risk-benefit ratio for her and her case, and I don't think this is just an individual case where you just say it's an anecdotal allergic reaction.

The literature will show that it's not an allergic idiopathic result. It's an expected complication of a drug used in a large population with the program that could have indicated the need for aggressive treatment and immediate cessation therapy, but those opportunities were lost because the publicity driving this drug, again, obliterates a scientific analysis and a full participation of doctors at the level they need to be.

Let me conclude by pointing out personally as a physician that I have long felt that patients

rely far too heavily on expensive, complex, and potentially toxic medications instead of using common sense and instead of using good health habits. Making the statins over the counter, particularly as regards certain statins that the panel will determine are pharmacologically different, potentially more hazardous than others, sends the wrong message to our society that there is a pill for every ill. You can smoke, but you can take care of it with a statin. You can eat at these nameless restaurants -- don't name names -- but you can take care of it with a statin pill.

It's interesting how we all come from our educational backgrounds and arrive at the end with a slightly different perspective. Dr. Anderson, who graduated from Harvard Medical School, four years, I think before I did, although we haven't checked our ages, has come up with a very different perspective. He has been enthusiastic about the pharmacologic measures that have improved our lives.

From the same school I was taught be very cynical about new drug developments. Be very cynical about what the manufacturers of these drugs have to say about the performance of the drug because you're the scientist, and the panel here being physicians, as

scientists themselves, will be making the decision.

I want to very lastly say that by way of the materials in that packet, my address, my name is there. This is a very short period of time, I think, for the panel to get all of the answers you necessarily want. I don't want to put you under pressure to ask me all of the questions you want to ask me if you have any or Mr. Calabio right now because I know we're over schedule.

I am very happy to augment my record, augment our report, and just be of help to any of the panel members or the panel generally at any time in the future.

Thank you.

Any questions for me or for Mr. Calabio, please, we'll entertain them.

DR. DeLAP: Well, I think we're all very sorry for the experience that Mr. Calabio and his family have gone through.

Do we have comments or questions from the family -- from the panel? Dr. Kweder.

DR. KWEDER: I have a question. Certainly you've provided a fair amount of literature to support that this particular event is out there and has occurred to other people. I think maybe it's fair to

say it's not a common event. To the individuals who are affected, that's no consolation at all.

DR. BARNETT: Well --

DR. KWEDER: There are other medications on the over-the-counter market that also have serious outcomes in small numbers of people. I can think of some, for example, some of the decongestants, and we could probably name many.

Do you think that all of those should not be over the counter, as well?

DR. BARNETT: No. I think that one of the better examples of this is acetaminophen, which caused Reyes Syndrome in children, and that certainly caused probably a death rate and an instance -- I'm sorry -- aspirin. Excuse me. Name, very important. Embarrass my professors from the past if I -- aspirin. Thank you.

And aspirin is far from coming off the market, but what did happen was as soon as the incidence became appreciated, that the warnings were far and wide, and the opportunity for physicians to intervene immediately upon notice of any inkling of this effect was present.

I fear that an OTC product like the statins, if not accompanied by a sufficiently well

balanced warning against the overt engagement of publicity and public persona to support it, in absence of that balance people won't be prepared to take the precautions when they are amongst the very few who will get ill, and I think that's mostly our warning here today.

Because it is quite possible that Mrs. Calabio would be alive today if she had stopped the pill and acted more aggressively for this disease that she had the moment that she had her side effect, and I really believe that she and her physicians, as the record will indicate, just didn't know it was coming.

And I think -- does that answer your question?

DR. DeLAP: I think, again, it's our expectation that products in the over-the-counter marketplace should be quite, quite safe and should provide a benefit that balances risks that there may be.

Of course, there aren't products that have no risks, and as long as we have an OTC marketplace, we have to try and make sure that the products that are there are as safe as they can possibly be, and that the risks that are attendant with their use are well communicated so, as you expressed, people can do

a good job of managing and minimizing the potential for harm.

Are there -- Dr. Temple.

DR. TEMPLE: Yeah. I just had one question. Obviously I hadn't looked at the cases you had before. Most of them appear to be single cases, and not many of them say that the relationship to the use of the drug was not obviously.

Is there any epidemiologic back-up of this? Just as an example, it's been possible to show the relationship of certain weight loss products to pulmonary fibrosis using epidemiologic methods. Of course, the risk there was relatively large. Anything like that here?

DR. BARNETT: What you've got is the results of my search using Medline and other library resources. I've got more material coming from the FDA through the Freedom of Information Act as to other reports, but none of them come to an epidemiologically significant report that the particular complication here of the pulmonary fibrosis is actually a public health issue, which is why it is kind of I hope -- I get the indulgence of the committee and they've had me here -- that it's important to put this kind of different perspective.

Everything has been epidemiological so far. I don't claim this is an epidemiological event. It may be in the aggregate a few lives lost are better than thousands of lives if that's what a certain drug leads us to. I haven't got --

DR. TEMPLE: No, I was wondering about the causality of the relationship. There are events that happen in the population without benefit of therapy, and so I was wondering how good the evidence was that it was causal.

DR. BARNETT: As to that, in terms of statistically, because we've had this question, for example, on breast implants, can you statistically connect the connective tissue disease. I don't have that information that there is that connection, that the incidence here isn't, in fact, the same as the population at large.

However, the articles that I've submitted, if you read them critically, do indicate there are indicia there which to the authors make it unmistakable in their minds that the statin was the direct cause of the syndrome. But I don't have anything to help you with the particular question.

DR. GILLIAM: Zocor is not one of the drugs that we will be considering for over-the-counter

status, and it is far more potent than the ones that we are considering. Do you have any indication that these ones that we will be considering would have the same side effect profile or would have less of a chance of causing these problems?

DR. BARNETT: Well, I concentrated my research on Simvastatin. However, the fluvastatin also, which I understand is a chemical which is nonorganically derived -- it's a produced chemical -- had a similar event occur, and across the board, all of the statins -- the answer to your question is, yes, I suspect that there's a problem will emerge over time if people use doses which are high and don't pay attention to the side effects because all of the statins do report what they call a lupus-like syndrome.

And the phenomenon here of the pulmonary fibrosis is a variant in the extreme manifestation within the pulmonary tree of a lupus-like syndrome amongst those people who end up with that lupus-like syndrome. So I would predict that over time if enough people use this drug, there will be a sufficient number of people getting pulmonary problems as well as lupus-type problems to raise alarms and, I think, to be of some concern.

DR. DeLAP: Well, thank you very much.

That concludes our session on the cardiology and cardiovascular drug class issues, and now we have a session on antimicrobials and antibiotic issues, and the first speaker is Kathleen Young for the Alliance for the Prudent Use of Antibiotics.

Is there someone here from the Alliance for the Prudent Use of Antibiotics?

(No response.)

DR. DeLAP: If not, we'll proceed to Gretchen Kidder, Alliance for Microbicide Development.

MS. KIDDER: Hi. I'm speaking here today on behalf of the Alliance for Microbicide Development. The alliance is a coalition of most of the major researchers and organizations involved in the development of microbicides, topical genital application being designed to help prevent sexually transmitted infections, STIs, very importantly including HIV.

It comprises developers from --

PARTICIPANT: We can't hear you.

MS. KIDDER: You can't hear me? Okay. Is this better?

It comprises developers from 34 biopharmaceutical companies, scientists from 26

nonprofit research institutions, and representatives of 20 health research and advocacy groups. The alliance is maintained with support from private philanthropies and accepts no federal funding.

The mission of the alliance is to accelerate the development and availability of microbicides for the millions of individuals globally who could benefit from them. The women of the world lead that list of potential beneficiaries for two primary reasons. The first is the feminization of the AIDS epidemic.

In the United States, women constitute the fastest growing group of those newly infected with HIV, and worldwide almost half of the almost 14,000 adults infected daily with HIV are women, with over 90 percent of those new infections being spread through unprotected heterosexual intercourse.

The second reason is that the currently most effective protection against HIV and most other STIs is the male condom. Yet since many men resist condom use, it is infrequent or irregular in many partnerships, and especially problematic where proven fertility is important or where couples want children despite their infectious status, as is often the case in developing countries.

Negotiating condom use or refusing unsafe sex may be particularly difficult in primary relationship partnerships where trust becomes an issue and in relationships where women are at risk of violence or abandonment.

We are talking about a population of many millions and a need that is relentless and immediate so that speed is of the essence in the development processes and in terms of practical availability once a produce has proved safe and efficacious in appropriately designed clinical trials. The assumption in much of the microbicide development and advocacy community has been that microbicides based on ingredients used mucosally for many years and generally recognized as safe, GRAS, but which represent roughly one quarter of the microbicides currently in development might reasonably be expected to go to market as over-the-counter products.

This view in no way excluded recognition that products dependent on totally new chemical entities, NCEs, would probably and appropriately require at least initial launch as prescription products, nor did this view imply any willingness to sacrifice safety for speed.

However, the possibility that all

microbicides might require initial prescription introduction has raised concerns about what that might mean for market readiness and the various dimensions of availability, importantly including cost, provider barriers, and physical access.

Because these hearings offer a proper venue for commentary and in order to present the perspectives of the microbicide community in a responsible way, this issue was discussed at the May 13th through 14th meeting of the alliance and was further addressed in a subsequent poll of those alliance participants who are developing products.

The following paragraphs present the results of those activities.

Consumer utilization of microbicides. There was consensus without exception that across the board and unrelenting prescription classification would hinder access and, therefore, microbicide utilization in a number of ways, and that the public health and individual human cost could be substantial.

In very practical terms, women in general could well find it more difficult to purchase microbicides on an as needed basis for routine prevention if they were not able to do so in an open marketplace, unconstrained by provider dependents.

The shared view was that product costs to consumers would inevitably be higher under prescription labeling added to which would be provider fees. The observation was made that sexual relations are not in themselves a disease requiring provider intervention, but rather decisions made by individuals on their own time.

The related comment was made that condoms are available over the counter for individual decisions by men without requiring the intervention of a learned intermediary by which token microbicides should be available over the counter for individual decisions by women.

Particular concern was expressed on behalf of women at risk. Such women are often disadvantaged by poverty, their position and social structures, and age, and might well be intimidated by those conditions and contained by possible stigma from seeking microbicides dispensed only by physicians or public health system providers.

Several respondents did note that there would also be market interest were prescription microbicides also to be available, partly deriving from the character of the product itself, partly deriving from the associated endorsement by the

medical community, partly deriving from a potential higher price.

Market intentions. Of 12 companies actively developing products, most of whom who have advanced beyond the preclinical phases, four are planning on over-the-counter introduction. Four foresee a prescription introduction followed by transition to over-the-counter status. One anticipates prescription classification, and two are unsure or undecided.

The issue of transition from prescription to over-the-counter status emerged as pivotal and is addressed below. Respondents were asked what the effect of determination to make all microbicides prescription products would have on their current plans and what effect such a determination might have on a prospective partner.

Because the overwhelming majority of those individuals and companies that are developing microbicides will be inevitably dependent on some kind of partnership to take their products forward, this consideration is not small. Of 12 developers, eight had either anticipated at least initial prescription status or felt that they could adjust to such a determination even if not anticipated, noting that

while the objective of reducing the spread of HIV compels them to continue, the requirement for a prescription classification would impose serious cost constraints and time line extensions.

However, of that group, five noted that the issue of status could make a difference to a prospective partner. One company felt that it would have to withdraw from the field altogether if initial OTC classification could not be anticipated, while four who might have to consider withdrawal would be able to stay in the field if there were a standard procedure for switching their product from prescription to OTC in a relatively brief period.

One creative proposal that emerged in the course of alliance discussions is the notion of developing a formal post introduction, post market consumer reporting system that could gather the kind of information the FDA would require for the transition from prescription to over-the-counter status.

This remains a germ of an idea that has already attracted interest as a subject worthy of pursuit and a topic for discussion with the agency itself.

The final question in the poll asked if

opposing criteria for regulatory decisions about status would be helpful. The sense of the responses was that attempting to establish such criteria in any fine grained way is premature. Although there was some agreement that microbicides based on currently marketed, over-the-counter or GRAS active ingredients or products based on components with long term safety records could reasonably be considered for initial over-the-counter classification, the point was made that some new chemical entities might prove to have a better toxicity profile than some older molecules and should not be disqualified from the outset simply because they were new.

From a richly textured discussion, however, two bottom lines emerged. The first was that determination about initial status should be made on a case-by-case basis.

The second was that any rigid, a priori decision about launch status for microbicides of the drug category should be assiduously avoided.

In conclusion, these opinions are based on a small sample, but the constituency represented and the weight of opinion within that constituency are not trivial. The core message from the microbicide community is an appeal to the Food and Drug

Administration for careful, but flexible and expeditious consideration of the merit and potential value of each microbicide against a background of urgent need among the very many who have no other protection from prospective death and disability.

Thank you.

DR. DeLAP: Thank you.

Comments? Questions?

Dr. Chikami.

DR. CHIKAMI: In your discussions with the people you polled or in your alliance, did you all consider the possible approach for those products which may already be over the counter, for example, for other indications, the approach of professional labeling for the microbicide indications and how that might impact their view of developing products in this area?

MS. KIDDER: I don't believe so, but we will.

DR. CHIKAMI: The other issue, I think, that you're appropriately pointed out, in fact, the products in this area represent are quite heterogeneous. Some of them, in fact, may be already on the market for other indications. Some of the development is involved in developing new chemical

entities for which there may be little, if any, clinical experience.

And I guess one of the issues relates to not only their safety profiles, but their effectiveness. Microbicides is a broad term, and in fact, the intention is to prevent a number of sexually transmitted infections, bacterial and viral and quite a diverse nature of viral infections.

And your views in regard to the appropriateness of these products for the OTC market, if in fact they may not be able to or their effectiveness against these very sexually transmitted infections, in fact, might not be uniform, for example, and how that might be appropriately communicated to the consumer.

MS. KIDDER: I'm not exactly sure, and I don't believe that I should be the person answering, but I would like to relay that question to our participants and get their feedback on that and add it to our written follow-up if that would be okay.

Thank you.

DR. DeLAP: Thank you.

Our next speaker is Dr. Thomas Moench from ReProtect, L.L.C.

DR. MOENCH: Thank you, Dr. DeLap.

I'm Thomas Moench, the Medical Director and a part owner of ReProtect, L.L.C.

ReProtect is a small pharmaceutical company developing a spermicidal microbicide gel intended to protect women against pregnancy, HIV, and other sexually transmitted diseases.

We thank the FDA for establishing the Microbicide Working Group to streamline the process of microbicide review. However, like other members of the microbicide development community, we were surprised and concerned when FDA staff announced in January at the preclinical microbicide workshop that all new microbicide-spermicide products might be classified as prescription drugs.

Our product, Buffer Gel, is made entirely of components that have been used mucosally for decades and are classified as GRAS, that is, generally recognized as safe. Buffer Gel maintains a protective vaginal acidity by maintaining a safe and effective concentration of protons in the vagina, and the buffering agent in Buffer Gel is Carbopol, a gel forming polymer that is used simply as an excipient in over 120 currently marketed pharmaceutical products, including at least nine products that are used vaginally.

Phase I studies show that unlike most existing spermicides based on detergents, intensive use of Buffer Gel does not disrupt cervical-vaginal epithelium. In this important respect, Buffer Gel appears to be safer than detergent based spermicides that have long been available OTC.

Unlike antibiotics discussed yesterday by Dr. Sparling, Buffer Gel has a low potential to encourage pathogen resistance since it simply maintains the naturally occurring vaginal acidity.

Other sponsors are developing microbicide products that have a similarly high expectation of safety. We believe that Buffer Gel and other microbicides based on low toxicity, nonabsorbable agents should be considered for direct approval for OTC use after adequate preclinical and clinical testing and with appropriate post marketing surveillance.

We believe that the public health impact of vaginal microbicides would be severely limited if they were restricted to Rx status since a woman is much less likely to use a microbicide if she must visit a physician to get a prescription. This is especially true for the very women who would most benefit from microbicides, the poor, the

disadvantaged, and the young.

Many women will be too embarrassed or too intimidated to obtain safer sex products from a physician. Sexually transmitted diseases and AIDS remain highly stigmatized in our society, and when a woman asks a doctor for a safer sex product, she may feel that she is telling her physician that she intends to engage in high risk sex. Women may wish to avoid such a conversation.

The argument might be made that hormonal contraceptives are widely used despite Rx classification and hence Rx status is not a severe barrier. This is an inappropriate analogy when applied to microbicides. Women understand and accept that they are at risk of pregnancy, and being a fertile woman carries no stigma.

In contrast, a woman who seeks to obtain a microbicide that's available only Rx must overcome a powerful stigma. She must reveal to others that she may be concerned she is having sex with an unsafe partner.

We recognize that the Rx only status may enhance detection of certain adverse events of new products that were not detected during clinical trials. We believe this might be an appropriate basis

for Rx classification of some of the new microbicides now being developed, but we believe that in its deliberations on OTC versus Rx status of vaginal microbicides, the FDA should consider not only the benefit of detecting those rare adverse events in users of the new product, but also the risk to public health if access to these products is limited by an Rx hurdle.

We ask the panel to consider the probable impact on public health if condoms were available only by prescription. Recall that condom sales increased substantially with the simple change of placing them on accessible displays rather than keeping them out of sight, behind the pharmacist's counter where they must be asked for.

This marketing experience shows that even the most minor barrier to access significantly limited the use of condoms. We believe that an Rx hurdle placed in the way of microbicides would much more dramatically limit their use by women.

We urge the panel to proceed on a case-by-case basis with microbicides and not to establish a categorical guideline that new microbicides/spermicides must initially be classified as prescription drugs.

Some new microbicides are composed of nontoxic ingredients with long track records of safe mucosal applications. Categorically imposing an Rx hurdle would risk the loss of major public health benefits, especially for those women most in need of vaginal products for safer sex.

Thank you for the opportunity to speak.

DR. DeLAP: Thank you.

Comments? Questions?

I have one question. When you described making products available with appropriate post marketing surveillance, what ideas might you have about appropriate post marketing surveillance?

DR. MOENCH: Well, I think the goal would be to detect adverse reactions that were rare enough that they weren't observed in clinical trials, and the kind of surveillance that could be envisioned would be either manufacturers or an organization like the Alliance for Microbicide Development, creating a registry for reporting of such events, possibly even having an 800 telephone number on all products so that women would be sort of actively encouraged to report events.

DR. DeLAP: Dr. Ganley.

DR. GANLEY: Yeah, I guess one of the

concerns has less to do with providing or the safety is what is the efficacy of these products, and we heard yesterday that you have to gear labeling down to a seventh grade education. So how can you adequately explain to a consumer that this treats certain sexually transmitted diseases or sexually transmitted diseases. It's not an absolute preventive, or should the requirement be that it's an absolute preventive?

I think that's really one of the main concerns as opposed to the necessary safety issues, but how do you provide this information, and what criteria should be used to say that something is effective?

I think the Rx -- one of the advantages of an Rx product are that there's an intermediary there to actually explain to a consumer, you know, what the down side is regarding effectiveness. So how do you overcome that?

DR. MOENCH: Well, I think it is an important question, and labeling of these kind of products is difficult and will require lots of thought and back and forth between the sponsors and the agency.

I wouldn't want to overestimate the difficulty of explaining to people that something can

give them partial protection. I think in all of our lives we know that. We wear seat belts. We have air bags. You might worry that gives people a false sense of security and encourages bad driving habits. Maybe that's true, but the benefits outweigh the risks of some misunderstanding some of the time.

So I do believe that consumers understand that there can be products that give them partial protection. In fact, I think most people in daily life know that that's the rule rather than the exception.

I do think it's going to bear emphasis on labeling, but I believe that that concept can be gotten across to consumers.

DR. GANLEY: Should there be certain diseases that we are more concerned about, for example, the transmission of HIV which could lead to a fatal outcome as opposed to other sexually transmitted disease which may have a morbidity, but not necessarily mortality associated with it?

DR. MOENCH: I think that's true, and I don't think that the labeling will have to do a lot to do that. When you look at the public's fears, it already lines up in those kind of ways. So I think it is true that a higher priority is placed by consumers

and product developers, and I would assume the agency for protecting against a disease like HIV.

DR. GANLEY: But getting to HIV, if you were able to share that there's a 50 percent reduction in transmission, there's still going to be a certain percentage of people out there that will develop an infection despite using the product, and I guess it gets back to how do you label that geared towards a seventh grade education.

DR. MOENCH: I think people with a seventh grade reading comprehension can understand the concept that this gives a 50 percent protection.

DR. DeLAP: Thank you very much.

Our next speaker is Dr. Kevin Whaley for EPIcyte Pharmaceutical.

DR. WHALEY: Can you hear me all right?

I'd like to thank the FDA for allowing me to speak to you today. My name is Kevin Whaley. I am representing EPIcyte Pharmaceutical. I'm also a member of ReProtect, the previous speaker, and I'm also a participant in the Alliance for Microbicide Development.

My purpose in requesting an opportunity to speak to the panel is that I wanted to give the panel sort of a view of the spectrum of products that we're

expecting that are coming out of the microbicide field. The Alliance for Microbicide Development has a range of products, and I think the products that were presented by Dr. Moench represent some products that, a class of products that actually may reasonably be considered to go OTC.

On the other hand, we have some things that are in the Alliance for Microbicide Development that are being considered, but are new chemical entities, but on the other hand, I would like to make the case that they may be considered for OTC or at least fast track switch.

I'm going to be using the products that we developing as sort of a case study. I think Buffer Gel is one example of one that might be considered for OTC application very early on, but I'm also very interested in giving you a view of what we believe may occur in terms of new chemical entities.

The molecules that I'll be talking about are antibodies. Antibodies I think the agency has a lot of experience with. They are being regulated primarily as therapeutics, but we believe that because of some new breakthroughs in the field, we believe that antibodies will be a relatively new area for prevention transmission, and I think we have to give

great consideration to technology that prevents the transmission of infectious diseases.

Ninety percent of all infections begin on a mucosal surface, and mucosal antibodies help prevent mucosal infections.

In terms of the comments about efficacy, I think there's been some data in animal studies that have shown that antibodies on mucosal surfaces do prevent disease, whether or not they're a virus or a bacteria or fungus or a parasite.

There are very few clinical trials, however, that have randomized double blind prospective clinical trials that have looked at this, but nonetheless, the prevention of transmission has been relatively impressive. It's enough to encourage us to continue to pursue this as a strategy.

We also feel fairly confident and because the agency has previously evaluated antibodies, and there are a large number of antibody products. We know a lot about the mechanism of action, and primarily on mucosal surfaces, it's agglutination, blocking of adhesion, and mucophylic trapping. It's a noninflammatory response, doesn't require most other components of the immune system.

Why this technology has not previously

been used in the prevention of disease -- you will have to remember that the immune system was developed to protect us from disease -- is because we have not previously had the technology to produce them at low cost and high capacity such as is required for OTC products.

That was recently done in 1995 where we were able to produce antibodies, human antibodies, and particularly secretory antibodies that go on mucosal surfaces in plants for low cost and large capacity production. These are very specific molecules, and we think they're very desirable from the point of view of microbicides.

So the plantibodies that we're talking about are going to be used as mucosal protectants. The plantibodies are human antibodies produced in plants at low cost and large capacity. They are purified from plants and formulated as pharmaceuticals, particularly, say, for example, for microbicides, and plantibodies will supplement and mimic the prevention that we already see with mucosal antibodies.

There's only been one clinical trial aimed at plantibody. That was recently reported in Nature Medicine. It was to treat Strep. mutans, an

ecological imbalance, and where we had six applications over 20 days, and the endpoint was to prevent recolonization.

The actual clinical efficacy was actually quite traumatic. The recolonization was prevented in four of four patients. There were no adverse side effects, and there were no serum antiplantibody responses. Admittedly this is very small numbers, and obviously large numbers of clinical trials need to be done with plantibodies, but our experience with antibodies and now beginning with plantibodies I think is very encouraging.

From EPIcyte's point of view, our first generation of products are going to be a lubricant that prevents sexual transmission of HSV2. We are developing a microbicide that prevents horizontal and vertical transmission of HIV.

We're also working not only on the genital-urinary tract, but also on the respiratory tract and for the gastrointestinal tract. We would like to see prevention, technology that prevents transmission much more widely used.

But I would like to spend the remaining amount of time that I have on the opportunities that we see in the microbicide field, the vaginal

microbicides.

We're primarily driven by the fact that in 1999, 15.4 million people in the United States acquired a new sexually transmitted disease, and it's a causative factor for infertility, pregnancy complications, cervical cancer, and infant mortality.

We're also driven by the fact that there's been a failure of imagination on the part of the scientific community in thinking about prevention of transmission of infectious diseases. Vaccines have clearly been thought about as a technology, but for all of the sexually transmitted diseases we do not have a vaccine against any of the sexually transmitted pathogens.

Also, the cures, at least for the viruses, are not -- we do not have tremendous therapeutic endpoints, and we are starting to see some drug resistance with some of these products.

In terms of some of the points that have been made about acceptability and efficacy, we're very enthusiastic about antibodies because that's their physiological role and because they are not absorbed as Dr. Moench mentioned about Buffer Gel, but also the fact that they're not really metabolized. They're not metabolized, and they're not broken down in a

significant way on mucosal surfaces.

That allows us to have a residence time that is dependent upon the mucous turnover time, and that allows one to think about products that have 18 to 24 hours' worth of protection. If one takes this half residence half time of an antibody, which was done in a study recently in reported in the Microbicides 2000 meeting, one can model what this might do in terms of acceptability.

If a woman were using this on a day-to-day basis and failed to use it on the fourth day, she still would have a significant level of antibodies in there, assuming we gave, because these are potent molecules, several half times of the molecule. We would still have protection on the second and perhaps even the third day. This is conjecture on our part, but this is preliminary data that is very intriguing to us.

From a regulatory point of view, because we've had a failure of imagination in the scientific community on thinking about mucosal protectants, we also do not want the regulatory entities to have a failure of imagination to think about how these products will be regulated.

The first generation will be similar to

things that have already been regulated, that is, there will be single antibodies against a single pathogen, but eventually we think the most promising mucosal protectants at least for antibodies will be multiple targets and with multiple antibodies.

I've used mucosal antibodies strictly as a case study. The Alliance for Microbicide Development does have a range of products. There are some that might be considered to go directly over the counter. We have some new chemical entities. I would like to think that we will continue to -- there's been a lot of discussion about a case-by-case basis. I would like to see that open even for new chemical entities if we involve the OTC regulatory people very early on in our process.

But talking generically about mucosal protectants, I think we need more technology in this category. Individuals are exposed to a range of mucosal pathogens on a daily basis. The strategy and technologies for preventing transmission of infectious diseases at mucosal surfaces is very limited, and because accessibility is important for personal protection, we believe that accessibility is a key issue, and we would like to see these things available as widely as we possibly can.

Thank you very much.

DR. DeLAP: Thank you.

Questions?

(No response.)

DR. WHALEY: Thank you.

DR. DeLAP: I think you covered things very well. Thank you.

Before we break, has Kathleen Young from Alliance for Prudent Use of Antibiotics returned?

Otherwise we're at our lunch break. It is currently ten minutes to one o'clock, and we'll try and reconvene here at 1:30, 40 minutes for lunch, 1:30.

Thank you.

(Whereupon, at 12:53 p.m., the meeting was recessed for lunch to reconvene at 1:30 p.m., the same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:44 p.m.)

DR. DeLAP: We're going to slightly change the sequence for Session 7 for the allergy and asthma drug issues, and under the revised plan, the first speaker will be Dr. Robert Seidman, Vice President, Pharmacy, Blue Cross of California.

DR. SEIDMAN: Thank you.

My name is Dr. Robert Seidman, and I am Vice President of Pharmacy for Well Point Health Networks based in Thousand Oaks, California.

Well Point Health Networks is one of the nation's largest publicly traded managed care companies serving the health care needs of over 7.5 million medical and approximately 31 million specialty members nationally.

Given our limited time today, I would like to take the opportunity to respond to the questions outlined by the FDA in the April 27th, 2000 Federal Register notice of this hearing.

Can you hear all right in the back?

In responding to these questions, I want to focus on the documented safety and effectiveness of the prescription nonsedating antihistamines Claritin and Alegra and the minimally sedating antihistamine

Zertec.

Through our prescription drug benefits, Well Point Health Networks currently provides access to these drugs at a copayment paid by the member.

There are three criteria that the FDA should consider in rendering decisions on over-the-counter availability of drug products: ease of self-diagnosis; ease of compliance with the treatment regimen; and drug safety.

In applying these three criteria to the second generation antihistamines referenced above, we have found that the average lay person can easily self-diagnose allergic rhinitis and treat the condition with relative issue.

This self-diagnosis and treatment is performed by millions of Americans daily with the current complement of over-the-counter antihistamines available.

The third criteria, safety, is also satisfied since hundreds of randomized controlled studies in the peer reviewed medical literature clearly show that these agents are safer than the currently available over-the-counter antihistamine alternatives.

To support our claim of second generation

antihistamine safety, we have also contracted with the University of Southern California School of Pharmacy to perform a meta analysis on all peer reviewed articles on antihistamines.

Our preliminary analysis of 84 peer reviewed articles clearly shows that the second generation antihistamines, Claritin, Alegra, and Zertec, are safer than those antihistamines that are currently available without a prescription.

The complete results of this analysis will be provided to the FDA as an amendment to our existing petition to convert these drugs to over-the-counter status.

The majority of Americans seek to self-medicate with over-the-counter drugs, and it is incumbent upon the FDA to insure access through OTC status of drugs that have documented safety, efficacy, and ease of use.

Regarding the treatment of chronic conditions, two interests must be balanced: potential harm of self-treatment versus the value of early diagnosis of a debilitating chronic disease.

It would also be beneficial for a portion of close to the $2 billion that are currently being allocated to direct-to-consumer advertising to be

redirected to efforts to help patients with the early diagnosis and treatment of disease states where our current medical interventions have been inefficient in improving the lives of Americans.

Diseases such as diabetes, asthma and hypertension are particularly amendable to greater health education. Drugs like antibiotics should not be available OTC because the current system of medical management has not succeeded in stemming the inappropriate prescribing of antibiotics and the resultant danger of increase in antimicrobial resistance.

Again, I want to focus on the safety and efficacy of the second generation antihistamines and not venture into the other more complicated classes of drugs. The second generation antihistamines clearly meet the criteria utilized by the FDA in determining whether a drug should be available over the country.

Consequently, they can be used as a model for other classes of drugs. When the marketplace, through direct-to-consumer advertising, converts a drug into a virtual over-the-counter drug, consumers can easily understand the benefits and risks of these products.

There is documented evidence demonstrating

that DTC advertising of second generation antihistamines has increase physician office visits to request prescriptions for these drugs, and that physicians are uncomfortable declining these requests.

As a result of this phenomenon, second generation antihistamines are virtual OTC drugs today. Even today we have examples of OTC and prescription versions of drugs in the same milligram and delivery system. So the issue of co-existing products is not new or novel.

Again, with a second generation antihistamines, there is no clinical controversy about converting these drugs to OTC status. When prescription drugs do go OTC, which I hope the second generation antihistamines will shortly do, the first drug converted is not necessarily the gold standard, although it would be difficult to imagine drugs safer and more efficacious than the currently available second generation antihistamines.

Personal consumer experience will determine which is the better drug. The question here is whether the pharmaceutical manufacturer has sole discretionary power to decide what is in the best interest of society. It is my belief that this important decision making process should be vested in

the clinical merits of these drugs and supported by the FDA.

The current structure for marketing OTC products in the United States is flawed. Currently no safe and effective drug has ever gone OTC without the pharmaceutical industry initiating the request for that conversion. In areas where controversy is nonexistent, as in the second generation antihistamines, the FDA should be proactive in providing easier access to these drugs. Maintaining Claritin, Alegra and Zertec as prescription drugs deprives the majority of patients ready access to the highest quality pharmaceutical care and trivializes the patient-physician relationship.

When there is no toxicity associated with a drug and a layperson can easily diagnose and treat a condition or disease, the FDA should take an activist role in converting those identified prescription drugs to OTC status.

As I indicated in our petition to the FDA, patients are seeking greater ownership of their health care and often prefer to self-medicate when feasible.

Of all the therapeutic classes of drug available, the discrepancy and safety between the current antihistamines available OTC compared to

prescription second generation antihistamines is most pronounced. The health care system should not be burdened with the increased cost and patient inconvenience associated with these drugs remaining prescription only.

The millions of allergy sufferers should have unimpeded access to these drugs as they do in Canada and in Europe. I request that the FDA review our petition and expedite the conversion of prescription Claritin, Alegra, and Zertec to OTC medication status.

At this time I would also like to present to the committee samples of these drugs from Canada and a receipt from the pharmacy showing the cost effectiveness of these agents and the labeling that is available in Canada.

Thank you.

DR. DeLAP: Thank you.

Can we keep these?

DR. SEIDMAN: Those are for personal use or getting you arrested.

(Laughter.)

DR. DeLAP: Just to start, how much experience do you think is enough with a new drug before it is contemplated for OTC use? I mean,

clearly we can say that when a new drug becomes available and there's not much experience with it, there may not be many safety reports, but that may just be that there isn't much experience and the drug may turn out to have some safety problems when we have more experience.

So how much experience or how do you think we should be measuring the amount of experience people have to have with a new drug before we can conclude that we know as much as we need to know to think about bringing it over the counter?

DR. SEIDMAN: My initial comment is that from our personal experience we are covering over 800,000 prescriptions of these agents a year, going back to when they were initially FDA approved. For this specific situation, I am personally comfortable with the amount of dosages that have been consumed by Americans.

Additionally, looking at the Canadian and European experience, there's a wealth of information on the safety and efficacy of these particular agents. I do appreciate the question as to when an FDA approved prescription drug is found to be safer than the already commercially available OTC products. What is the appropriate time frame to be determined?

And I would really be, you know, more comfortable deferring that decision to the clinicians within the FDA to who are reviewing basically similar data that we are reviewing today in the peer reviewed literature.

DR. DeLAP: Dr. Cantilena.

DR. CANTILENA: I just have a couple of questions. One with regard to access from your subscribers, if these drugs were over the counter, would they have a copay, you know, situation in terms of, you know, the over-the-counter status? Would it cost the subscriber any more money to use them over the counter?

DR. SEIDMAN: The sole intent of our petition was to increase access to health care, and in all of the financial modeling that we have done in comparing these products' costs in the United States, in Europe, and in Australia, in U.S. dollars, and specifically in referencing the visual aids that I have presented to the committee, one month's supply of Claritin in Canada in U.S. dollars is 11, $11 per patient, per month.

In managed care plans, the average brand copay probably ranges from ten to $20 per month per prescription. We do not believe that there will be an

additional out-of-pocket cost for these agents when they are converted to OTC status because of the competition in the marketplace between the three pharmaceutical manufacturers.

I believe that the cost effectiveness of converting these drugs to over-the-counter status can really be answered in three ways. First, unfortunately, there are millions of people in the United States, unlike those who are in the room today, who do not have any health insurance, who are paying totally out of pocket for their office visit to see their physician. They are paying totally out of pocket at 50 to $60 per month for these prescriptions.

For those people who are uninsured, having these products available at $11 per month is in their best interest.

We also have a tremendous number of people who are uninsured who would like to be insured, and removing these products from the prescription drug product gives health plans greater flexibility in pricing, in creating these products to make them more affordable.

And thirdly, removing these products from prescription status allows us to focus our energies on those therapeutic classes of drugs that really do

require the analysis and the care management to insure that we obtain appropriate outcomes in our patients with diabetes, hypertension, et cetera.

DR. CANTILENA: So in follow up, if -- I think I hear you saying that it's a wash from the subscriber point of view in terms of cost, and in terms of from the, you know, perspective of the health care network is that, you know, financially advantageous to have it OTC versus prescription other than allowing you to focus your efforts on these other, you know, disease categories.

DR. SEIDMAN: We currently are experiencing a crisis in health care, and that is prescription drug costs are increasing at 15 to 20 percent per year. Some employer groups that have a larger retiree population are now spending 25 percent of their total health care dollars on prescription drugs.

Retaining these products as prescription is inherently inefficient. Moving them to over the counter status will free health plans and provide greater access to consumers to these agents.

DR. DeLAP: Dr. Temple.

DR. TEMPLE: Not that this is something we necessarily think about, but nothing would actually